UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/646,970 | 08/21/2003 | Carol J. Phelps | 10758.105009 | 3048 |

20786 7590 10/03/2008

KING & SPALDING LLP
1180 PEACHTREE STREET
ATLANTA, GA 30309-3521

| EXAMINER | |
|---|---|
| SGAGIAS, MAGDALENE K | |
| ART UNIT | PAPER NUMBER |
| 1632 | |
| MAIL DATE | DELIVERY MODE |
| 10/03/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/646,970 | PHELPS, CAROL J. | |
| | Examiner | Art Unit | |
| | MAGDALENE K. SGAGIAS | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-21,43-46 and 48-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) ____ is/are allowed.

6)☒ Claim(s) *1-18,43-46 and 48-65* is/are rejected.

7)☒ Claim(s) *19-21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 July 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/21/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's arguments filed 5/16/08 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1-21, 43-46, 48-65 are pending and under consideration. Claims 22-42, 47 have been canceled.

### *Allowable Subject Matter*

Claims **19-21** are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims **1-16, 51-59, 61, 63-64** rejection under 35 U.S.C. 102(a) as being anticipated by **Lai et al,** (Science, 295: 1089-1092, February 2002) is withdrawn in view of Applicants

arguments that the alpha(1,3)GT piglets produced by Lai et al still expressed alpha(1,3)GT as shown by later studies coming out from the same group.

Claims **8, 13, 48-50** rejection under 35 U.S.C. 102(b) as being anticipated by **Gustafsson et al,** (6,153,428; Nov 28, 2000) is withdrawn in view of Applicants arguments that Gustafsson did not actually make any cells lacking expression of a-Gal and Gustafsson provides only prophetic examples for possible methods of making such cell.

Claims **1-16, 43-44, 46, 48-49** rejection under 35 U.S.C. 102(e) as being anticipated by **Denning et al,** (US 7,126,039 B2, Date of Patent: Oct. 24, 2006; Filed: Mar. 21, 2002) is withdrawn in view of Applicants arguments that Denning teaches reduction to practice sheep alpha-1,3-GT cells and not pig cells

Claims **1-8, 13, 17-18, 43, 48, 60, 62** remain rejected under 35 U.S.C. 102(e) as being anticipated by **Hawley et al,** (US 2006/0242722 A1) for the reasons of record of the previous office action mailed 11/16/08.

Applicants argue that the priority document of Hawley, US Provisional Application No. 60/403,405, which does not include the production of viable animals using any technique, and thus does not provide any indication that this reference anticipates the claimed invention more than the other references cited. Applicants argue the pigs in Hawley post-date the pigs produced by the present inventors. As noted in the attached New Scientist news release dated January 13, 2003 and entitled "Mini-pig clone raises transplant hope", the pigs from Hawley's lab at Immerge were born in November, 2002 whereas the pigs that are the subject of the present invention were born in July, 2002. The article notes that "[h]owever, Goldie is not the first double-knock-out pig to be cloned." Hawley therefore does not predate the present application for the relevant information, which is the production of viable pigs lacking any

expression of functional alpha-1, 3-GT. Applicants respectfully request that the Examiner withdraw the above rejections as no prior art reference provides pigs that lack alpha-1,3-GT expression by any method, but merely provide prophetic examples of production of such animals. As discussed previously and again below, the production of any pigs lacking alpha-1, 3-GT would have been considered highly speculative prior to the present invention because one of skill in the art would have believed that the pigs would be developmentally compromised and that the lack of a major sugar, specifically alpha-1, 3-GT on the surface of all pig cells would have been lethal.

These arguments are not persuasive because: A) the cited reference by Hawley et al, (US 2006/0242722 A1) claims priority of the US Provisional Application No. 60/403,405, August 14, 2002 which is before the claiming priority of August 21, 2002 of the instant application. The US Provisional Application No. 60/403,405, August 14, 2002 does not need to provide reduction to practice of the invention. Hawley et al, teach the production of piglets using cell clones lacking wild-type $\alpha$1,3-Galactosyltransferase (GGTA1), wherein the expression of the $\alpha$1,3-Galactosyltransferase activity in the GGTA1 null animals was negative, organs and cells from said null pigs. C) The claimed invention is not limited to the production of homozygous $\alpha$(1,3) galactosyltransferase pigs by nuclear transfer by knocking out one allele of the $\alpha$(1,3) galactosyltransferase gene first by conventional targeted homologous recombination-mediated disruption, but relying on selection of a natural mutation on the second allele of the porcine $\alpha$(1,3) galactosyltransferase gene, in order to produce the claimed pigs and the invention as claimed reads on any $\alpha$1,3-Galactosyltransferase null pig via any method of creating said pig, therefore the production of piglets by Hawley using cell clones lacking wild-type $\alpha$1,3-Galactosyltransferase, wherein the expression of the $\alpha$1,3-Galactosyltransferase activity in the

α1,3-Galactosyltransferase null animals was negative, organs and cells from said null pigs anticipates the claimed invention thus, the rejection is maintained.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims **1-18, 44-46, 49-59, 61, 63-65** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Lai et al,** (Science, 295: 1089-1092, February 2002) in view of **Straham et al,** (Frontiers in Bioscience, 1, e34-41, 1996).

Lai teaches the production of four live pigs in which one allele of the α-1,3-galactosyltransferase locus has been knocked out by nuclear transfer cloning, wherein clonal fetal fibroblasts cell lines were used as nuclear donors for embryos reconstructed for enucleated pigs (abstract and thru ought the document). Lai teaches the knock out of a α1, 3-Galactosyltransferase (GGTA1) locus of exon 9 (figure 1). Lai teaches the next step will be to create α1, 3-Galactosyltransferase (GGTA1)-null (honmozygous knock out pigs) by breeding from their reported produced pigs (p 1092, 1st column, 2nd paragraph). Lai have suggested the availability of galactosyltransferse-null pigs will allow a clearer evaluation of approaches currently in development aimed at overcoming potential delayed and chronic rejection mechanisms in porcine xenotransplantation (p 1092, 1st column, 2nd paragraph). Lai differs from

the claimed invention by not teaching the breeding of the GGTA1 heterozygous pigs producing, homozygous pigs and cells, tissues or organs obtained from GGTA1 homozygous pigs for use as an ex vivo or in vivo supplement or replacement for recipient cell, tissues, or organs.

However, at the time the claimed invention was made, Strahan et al teach the α(1,3) galactosyltransferase epitope is the major target for human anti-pig natural antibodies leading to the events that precipitate the hyperacute rejection (p 38, 2nd column, 1st paragraph). Strahan teaches attempts are being made to produce transgenic pigs with reduced levels of expression of the α(1,3) galactosyltransferase epitope (p 37, 2nd column, 1st paragraph). As such, Strahan et al provide sufficient motivation for one of ordinary skill in the art to breed the heterozygous α(1,3) galactosyltransferase pigs produced by Lai in order to obtain homozygous pigs with no expression of the α(1,3) galactosyltransferase.

Accordingly, in view of the teachings of Strahan et al, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to breed the heterozygous knockout pigs of Lai with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a breeding of said pigs particularly since Strahan teaches the need for the α(1,3) galactosyltransferase null epitope tissues, cells and organs for xenotransplantation and particularly since Lai have suggested the availability of galactosyltransferse-null pigs will allow a clearer evaluation of approaches currently in development aimed at overcoming potential delayed and chronic rejection mechanisms in porcine xenotransplantation.

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Applicants argue the Examiner asserts that, although Lai produced only heterozygous pigs, Straham provides the motivation to breed homozygous knock out pigs because it indicates

that the a-Gal epitope was likely a major target for human anti-pig antibodies. As noted previously, Applicants do not assert that they were the first to believe that α-Gal null animals would be useful if it were possible to make viable animals, merely that they were the first to overcome the expectation that these animals were non-viable and thus were the first to pursue techniques that would lead to successful production of living animals that lacked functional a-Gal. Without a reasonable expectation that a combination of references would lead to success, the ordinarily skilled artisan would not combine these references. Applicants respectfully request withdrawal of this rejection.

These arguments are not persuasive because Lai teaches the production of a-1,3-galactosyltransferase heterozygotes and also teaches the next step will be to create a-1,3-galactosyltransferase–null (homozygous knockout) pigs, either by breeding to a heterozygous male produced by nuclear transfer or by sequential nuclear transfer modification of cell lines produced from the four female pigs produced by Lai (p 1092, 1st column, last paragraph). Because a-1,3-alactosyltransferase–null mice have already been produced, it is not anticipated that this genetic modification will be lethal in the null animals. Lai suggests that a-1,3-galactosyltransferase–null pigs will not only eliminate hyperacute rejection but also ameliorate later rejection processes, and (in conjunction with clinically relevant immunosuppressive therapy) will permit long-term survival of transplanted porcine organs (p 1092, 1st column, last paragraph). At a minimum, the availability of galactosyltransferase-null pigs will allow a clearer evaluation of approaches currently in development aimed at overcoming potential delayed and chronic rejection mechanisms in porcine xenotransplantation (p 1092, 1st column, last paragraph).

since the claimed invention is not limited to the method of **(a)** for making homozygous α(1,3) galactosyltransferase pigs by nuclear transfer by making porcine fetal fibroblasts

homozygous for inactivated α(1,3) galactosyltransferase (GT) gene, by toxin A, wherein first allele was knocked out by conventional targeted homologous recombination-mediated disruption, but relied on selection of a natural mutation on the second allele of the porcine α(1,3) galactosyltransferase gene, wherein the mutation comprises the presence of a T-to G point mutation in an allele at the second base of exon 9 of the α(1,3) galactosyltransferase gene; and **(b)** breeding a male pig heterozygous for the alpha 1,3 GT gene with a female pig heterozygous for alpha 1,3 GT gene, wherein first allele was knocked out by conventional targeted homologous recombination-mediated disruption, but relied on selection of a natural mutation on the second allele of the porcine α(1,3) galactosyltransferase gene, wherein the mutation comprises the presence of a T-to G point mutation in an allele at the second base of exon 9 of the α(1,3) galactosyltransferase gene Lai/Stahan is an exemplified prior art that teaches that it is routine or well-established in the art to breeding of the GGTA1 heterozygous pigs producing, homozygous pigs and cells, tissues or organs obtained from GGTA1 homozygous pigs for use as an ex vivo or in vivo supplement or replacement for recipient cell, tissues, or organs for xenotransplantation. Strahan et al teach the α(1,3) galactosyltransferase epitope is the major target for human anti-pig natural antibodies leading to the events that precipitate the hyperacute rejection; teaches attempts are being made to produce transgenic pigs with reduced levels of expression of the α(1,3) galactosyltransferase epitope and as such, Strahan et al provide sufficient motivation for one of ordinary skill in the art to breed the heterozygous α(1,3) galactosyltransferase pigs produced by Lai in order to obtain homozygous pigs with no expression of the α(1,3) galactosyltransferase. Therefore, the rejection is maintained.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims **19, 44-46, 49-50,** rejection under 35 U.S.C. 112, first paragraph is withdrawn in view of the amendment.

**Claims 19-21 appear to be free of the prior art of record but are depended from rejected claims.**

***Conclusion***

**No claim is allowed.**

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FIAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Magdalene K. Sgagias, Ph.D.
Art Unit 1632

/Anne-Marie Falk/
Anne-Marie Falk, Ph.D.
Primary Examiner, Art Unit 1632